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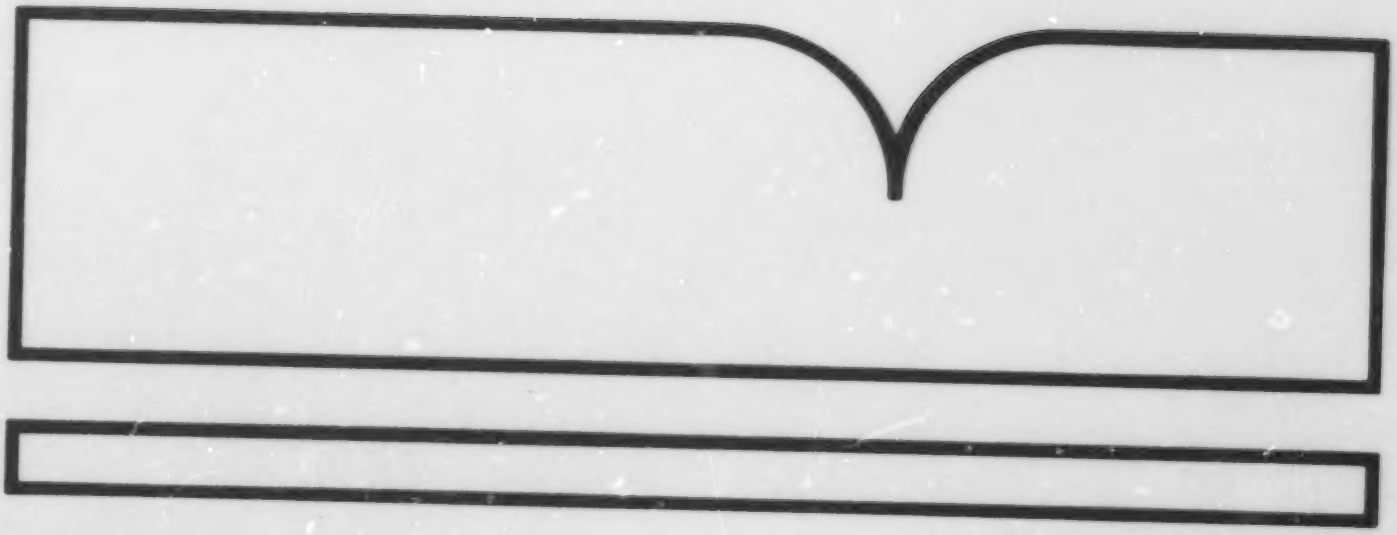

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16. ABSTRACT

Forty-nine children aged 6 to 12 years were evaluated for residual effects of lead exposure using psychometric, electrophysiological, and medical tests five years after initial assessment. The original range of blood lead (PbB) levels was 6-59 ($\bar{x}$=28) µg/dl; the current range was 6-30 ($\bar{x}$=14) µg/dl. A linear relationship between PbB and slow brain wave voltage during sensory conditioning was observed at initial evaluation (Otto, et al., 1981) and at two-year follow-up (Otto, et al. 1982). No significant relationship between PbB and slow wave voltage during passive conditioning was found at five-year follow-up, although a linear increase in slow wave negativity relative to current PbB level during active conditioning was suggested by exploratory analyses. Another exploratory analysis revealed a significant linear relationship between original PbB level and the latency of waves III and V of the brainstem auditory evoked potential. The latency of both waves increased as a function of original PbB. Increased latency of these waves is suggestive of subclinical pathology of the auditory pathway rostral to the cochlear nucleus, although end-organ impairment cannot be ruled out. No threshold for the effect of Pb on auditory function was apparent.

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JOURNAL ARTICLE

5-Year Follow-up Study of Children with Low-to-Moderate Lead Absorption: Electrophysiological Evaluation[1]

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Forty-nine children aged 6 to 12 years were evaluated for residual effects of lead exposure using psychometric, electrophysiological, and medical tests 5 years after initial assessment. The original range of blood lead (PbB) levels was 6–59 ($\bar{x}$ = 28) μg/dl; the current range was 6–30 ($\bar{x}$ = 14) μg/dl. A linear relationship between PbB and slow brain wave voltage during sensory conditioning was observed at initial evaluation and at 2-year follow-up. No significant relationship between PbB and slow wave voltage during passive conditioning was found at the 5-year follow-up, although a linear increase in slow wave negativity relative to the current PbB level during active conditioning was suggested by exploratory analyses. Another exploratory analysis revealed a significant linear relationship between the original PbB levels and the latency of waves III and V of the brainstem auditory evoked potential. The latency of both waves increased as a function of original PbB. Increased latency of these waves is suggestive of subclinical pathology of the auditory pathway rostral to the cochlear nucleus, although end-organ impairment cannot be ruled out. No threshold for the effect of Pb on auditory function was apparent. © 1985 Academic Press, Inc.

INTRODUCTION

The basic objective of this study was to determine if asymptomatic lead exposure in early childhood results in altered central nervous system (CNS) function in children when they reach school age. This study was a 5-year follow-up evaluation of children originally assessed in 1977–1978. Original blood lead (PbB) levels ranged from 6 to 59 μg/dl. Previous evaluations (Otto *et al.*, 1981, 1982) indicated that slow brain potentials elicited from young children during sensory conditioning varied systematically with body Pb burden in a manner that persisted for at least 2 years. In the 5-year follow-up study, the same sensory conditioning task as well as other clinically proven tests of sensory function (auditory brainstem and pattern-reversal visual evoked potentials) were used to assess the persistence of previously observed CNS effects and to clarify the functional significance of these findings.

The brainstem auditory evoked potential (BAEP) is widely used in clinical neurology to assess the integrity of the auditory pathway and to diagnose non-

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specific demyelinating disease such as multiple sclerosis (Starr *et al.*, 1978; Aminoff, 1980). The pattern-reversal visual evoked potential (PREP) has also been used extensively for neurological assessment of the visual system and multiple sclerosis (Halliday *et al.*, 1972, 1973). The PREP is more sensitive than the flash evoked potential (FEP) in most human testing applications (Halliday and McDonald, 1981). In view of the ease of administration and interpretation, stability, reliability, sensitivity to neurological insult, culture-free nature, and relative age independence of the BAEP and PREP, these measures are well suited for pediatric neurotoxicity testing (Otto, 1981).

The utility of the BAEP in neurotoxicity testing has been demonstrated in animal models. Increased BAEP latency following hexane exposure (Rebert and Sorenson, 1983) and decreased BAEP amplitude following toluene exposure (Rebert *et al.*, 1983) were found in rats. BAEPs have been employed in at least one pediatric lead study: Guerit *et al.* (1981) reported no effect of lead exposure on a composite neurophysiologic score that included BAEP, FEP, and EEG in children living near a smelter. The lack of detail about the derivation of composite scores and statistical analysis, however, precludes any meaningful interpretation of these data.

A variety of lead effects on visual function in animal models has been reported. Fox *et al.* (1977) observed increased latencies of visual evoked potentials (VEP) in rats neonatally exposed to Pb. VEP abnormalities persisted in these rats when they reached adulthood. Decreased conduction velocity in visual pathways of suckling Pb-exposed rats has been reported by Cooper *et al.* (1980) and Impelman *et al.* (1982). Impairment of scotopic function in young rhesus monkeys (Bushnell *et al.*, 1977) and suckling rats (Fox and Wright, 1982) exposed to Pb has also been observed.

PREPs have been used by Sborgia *et al.* (1983) and Ewert *et al.* (in press) to study the effect of lead exposure on visual function in humans. Sborgia *et al.* observed increased PREP latency in lead workers compared to nonexposed controls. Ewert *et al.* reported an inverse relationship of PbB and PREP latency in children living near a lead smelter.

METHODS

Subjects. Forty-nine children (26 boys) aged 6 to 12 years participated in this study. All but one child were from low-income black families considered to be at risk for lead poisoning (Mahaffey *et al.*, 1982). Lead exposure sources included lead dust inadvertently transmitted into homes on the clothing of parents who worked in a battery factory or peeling Pb paint in the children's homes. All children were previously evaluated in 1977–1978. Children were carefully screened to ensure that there was no evidence of birth trauma, congenital abnormality, significant disease history, or overt symptoms of lead poisoning. A thorough medical history of children was again obtained from mothers to update records since the previous evaluation. A pediatric and neurological examination was performed on the day of testing to determine the child's current health status and to identify any overt symptoms of neurological impairment. Data were not used from children with any major illness or who were taking medication.

Blood lead (PbB) measurements. Blood lead measurements were carried out at the Toxic Metals Laboratories, Pathology Department, University of North Carolina. The Ediger and Coleman (1972) modification of the Delves Cup micro atomic absorption spectrometric procedures (Delves, 1970) was employed for analysis. Quantitation was by the method of addition using blood of known lead content and electronic integration of the signal (Hewlett–Packard Model 3300). External quality control checks included participation in the CDC lead testing proficiency program and a multilaboratory analysis of blood lead with Environmental Sciences Associates and the New York City Health Department laboratory in connection with another study (Piomelli *et al.*, 1980). Internal quality control included use of certified blood lead samples from a commercial laboratory (Kaulson Laboratories) and the New York State Health Department.

Testing facilities. Electrophysiological data were recorded in a mobile laboratory provided by USEPA. Psychometric evaluations and medical examinations were done in a trailer obtained from the University of North Carolina. The mobile laboratory and trailer were located adjacent to the Wake County Health Center to facilitate access by the subject population.

Passive sensory conditioning. In this test the children watched a silent cartoon. At random intervals of 7 to 13 sec (mean of 10 sec), a 100-msec, 8-kHz, 90-dB SPL tone (conditioned stimulus, CS) was presented via loudspeaker. After a 1400-msec interstimulus interval, an unconditioned stimulus (UCS)—a 1500-msec blanking of the cartoon—occurred. Children were told that the tone and video blackout would occur, but that they should continue to watch the TV screen since the cartoon would continue after a very short time. A total of 100 trials was presented. On-line averages of trials 1–50 and 51–100 were obtained to assess temporal change in brain wave patterns during conditioning. Single trials were saved for off-line editing and analysis. This test took about 18 min.

Active sensory conditioning. The same stimuli were presented at the same intervals except that the video blackout was lengthened to 3 sec. Children were also presented with a button and instructed to press the button as rapidly as possible as soon as the cartoon went off. The cartoon reappeared as soon as the button was pressed (or after 3 sec had elapsed). Children were given five practice trials with considerable verbal reinforcement to ensure that they understood the task and that they responded rapidly. Fifty test trials were then recorded and averaged on-line. This test took about 10 min.

EEG/EOG recording procedures. Videotaped cartoons presented on a television console were used to engage the attention and to minimize eye and body movements of children during sensory conditioning. EEG was recorded from silver chloride pellet electrodes placed at standard midline scalp locations over frontal (Fz), central (Cz), and parietal (Pz) cortex. These leads were referred to linked mastoid (A1, A2) electrodes. Electrodes were also placed above and below the right eye for monitoring and editing eye movement artifact. To minimize EEG noise, the scalp was abraded with OmniPrep. Electrode impedance below 10 kohm was required to commence recording. In most cases, impedance was below 2 kohm. Individual conditioning trials were manually edited to minimize eye movement artifact and to eliminate blocking artifact. Trials were rejected if EOG

artifact was reflected in the vertex recording. Slow wave voltage was measured during the 1-sec interval preceding UCS onset (relative to baseline voltage measured as the mean voltage of the 1-sec pre-CS interval) for confirmatory hypothesis testing. The 1-sec interval was further divided into two 500-msec segments for post hoc exploratory testing in more detail.

Brainstem auditory evoked potential (BAEP). The BAEP was recorded at a bandpass of 100–3000 Hz and sampled at 50 kHz. Two replicate averages of 2000 binaural clicks of alternating polarity were obtained using a Cz-A1,A2 derivation. Clicks generated by a Grass S10CTCM control module were presented at 60 dB above the 2-kHz pure tone threshold of each child as determined by audiometric testing prior to BAEP recording. Alternating polarity was used to minimize stimulus artifact and the cochlear microphonic. A stimulus rate of 10.9 clicks/sec was used to minimize 60 Hz artifact. In order to minimize muscle artifact, children were tested lying down in the darkened van. Children were instructed to close their eyes, and relax their muscles, and were encouraged to go to sleep. Most children, in fact, fell asleep. A vertex-positive or mastoid-negative event produced an upward deflection. Latencies of upward deflections of waves I, III, and V and interpeak latencies (V-I, V-III, and III-I) were measured. BAEP testing took about 15 min.

Pattern-reversal evoked potentials. A pediatric pictorial eye chart was used to check visual acuity before testing. Subjects were seated at a distance of 5 ft from a Grass visual pattern generator (VPG-1) set for full field presentation of 24-min checks at 2 reversals/sec. The luminance of the VPG screen was adjusted to obtain 90% contrast of light and dark squares under subdued lighting test conditions. A Pz–Cz derivation was recorded using a 1- to 300-Hz bandpass and a 2-kHz sampling rate. Two hundred trials were averaged to obtain stable binocular waveforms. Two replications were obtained. Four measures were obtained for each waveform: latencies of N1, P1, and N2 components and N1P1 amplitude. The PREP assessment took about 7 min.

Statistical analyses. A single confirmatory hypothesis that slow wave (SW) voltage during passive sensory conditioning varies as an interactive function of original PbB levels (recorded in 1977–1978) and age was tested using a multivariate regression model described previously (Otto *et al.*, 1981). A modified multivariate regression strategy was used for exploratory analyses of other SW, BAEP, and PREP measures. The exploratory model included PbB, five control variables [age, SES, gender, maternal IQ, and HOME, which indexes the quality of home caregiving environment (Caldwell and Bradley, 1979)], and the interactions of PbB with each control variable. The first step in each exploratory analysis was to test the set of interactions. If the set was nonsignificant, all interactions were dropped from the model. The second step was to test main effects of the set of control variables. If any interaction or main effect of a control variable was significant, this factor was retained in the model. The third step was to test for the main effect of PbB. The resultant multivariate model was then further reduced in the same stepwise manner for individual or linear combinations of response variables.

RESULTS

PbB levels. The current range of PbB levels was 6 to 30 μg/dl (mean = 14). The correlation of original (PbB1) and current (PbB5) PbB values was 0.74.

Passive sensory conditioning. Table 1a shows the mean and standard error of SW voltage averaged across subjects at different recording sites during early (1–50) and late (51–100) trials. The 1-sec SW measurement interval was also divided into two half-second epochs (500–1000 msec and 1000–1500 msec). Results, illustrated in Fig. 1, indicated that SW negativity was greater during early than late trials, was greater during the first than the second half-second measurement epoch, and was larger at frontal and central than parietal recording sites. These differences controlling for PbB levels were significant as shown in Table 1b.

In order to test the confirmatory hypothesis that SW voltage varies interactively with age and original blood lead level, vertex (Cz) measures were averaged across all trials and measurement epochs. Results of the confirmatory analysis are shown in Table 2. Slow wave voltage recorded at the vertex during passive sensory conditioning did not vary interactively with original PbB and age.

Exploratory analyses were also done to examine in more detail the relationship of SW voltage, original and current PbB, and possible confounding variables at different recording sites during early and late trials. Multivariate tests for interactions and main effects were not significant in any analyses using either original or current PbB values, although some univariate tests indicated significant interactions (PbB1 × MIQ, PbB5 × sex, PbB5 × HOME) at Cz or Pz during late

TABLE 1

SLOW WAVE VOLTAGE DURING PASSIVE SENSORY CONDITIONING: SAMPLE MEANS AND EXPLORATORY ANALYSIS OF RECORDING SITE, TRIALS, AND MEASUREMENT EPOCH

(a) Mean and standard error of slow wave voltage (μV)

	Trials 1–50		Trials 51–100	
	Epoch		Epoch	
Site	500–1000	1000–1500	500–1000	1000–500
Fz	−4.32, 0.65	−2.10, 0.57	−3.40, 0.56	−1.08, 0.55
Cz	−4.44, 0.57	−2.08, 0.58	−2.46, 0.45	−0.55, 0.55
Pz	−0.51, 0.57	−0.36, 0.56	0.44, 0.38	0.98, 0.50

(b) Multivariate contrasts of dependent variables

Effect	F	P	df_N, df_D
Site × epoch × trials	3.94	0.026	2,45
Site × epoch	35.89	5×10^{-10}	2,45
Site × trials	1.96	0.15	2,45
Epoch × trials	0.00	0.98	1,46
Site	42.95	4×10^{-11}	2,45
Epoch	36.46	3×10^{-7}	1,46
Trials	4.47	0.04	1,46

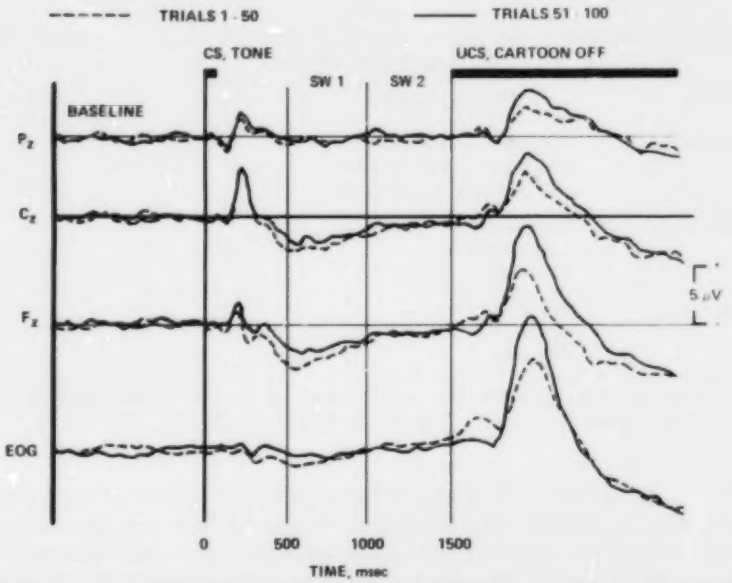

FIG. 1. Summary averages of slow potentials observed at frontal (Fz), central (Cz), and parietal (Pz) recording sites in children during passive sensory conditioning. The electro-oculogram (EOG) recorded from electrodes above and below the right eye of subjects is also shown. Horizontal bars above averages depict the intervals during which conditioned (CS) and unconditioned (UCS) stimuli were presented. Averages for early (1–50) and late (51–100) trials are superimposed. Measurement intervals (SW1 and SW2) are delimited by vertical lines.

trials. The complex and exploratory nature of these findings does not warrant further elaboration until further study has been completed.

Active sensory conditioning. Table 3a shows the mean and standard error of slow wave voltage averaged across subjects at different recording sites during active sensory conditioning. SW negativity was substantially larger during active than passive conditioning. The anteroposterior distribution of SW voltage, illustrated in Fig. 2, showed a sharper gradient in the active than passive task with a clear frontal maximum. Furthermore, the duration of SW negative shifts was much longer in the active than passive condition. Statistical results are summarized in Table 3b.

Exploratory multivariate analyses were conducted to assess the relationship of SW voltage, PbB1, PbB5, age, and other demographic variables during active conditioning. A significant main effect of current PbB was observed at Fz, Cz, and Pz in the second half of the measurement interval (1000–1500 msec). Results are shown in Table 4 and Fig. 3. The main effect of original PbB was significant only at Pz.

Brainstem auditory evoked potentials. Hearing thresholds as determined by audiometric screening did not vary significantly with original PbB levels. Table 5 indicates the mean, standard error, and range of BAEP measures observed in

TABLE 2
RESULTS OF CONFIRMATORY ANALYSIS OF MEAN SLOW WAVE VOLTAGE AT THE VERTEX DURING PASSIVE CONDITIONING[a]

Effect	Effects included	F	P	df_N, df_D
Interaction	Age linear × lead linear Age linear × lead quadratic Age quadratic × lead linear	0.42	0.74	3,38
Original lead	Lead linear Lead quadratic Lead cubic	1.18	0.33	3,41
Age	Age linear Age quadratic Age cubic	0.85	0.47	3,44

[a] SW voltage was averaged across early and late trials (1–100) and across measurement epochs (500–1500 msec). Mean SW voltage: −2.46 μV; standard error: 0.35 μV. α = 0.5.

children. Table 6 summarizes the results of exploratory multivariate and stepdown analyses done to evaluate the relationship of original PbB, possible confounding variables, and BAEP measures. No significant interactions were observed in multivariate comparisons. Main effects of sex (latencies of waves III, V, and V-I), original PbB (III and V), and HOME (wave V only) were significant. Male latencies were longer than female latencies. Wave III and V latencies increased linearly with original PbB. The partial r^2 values for PbB1 were 21.2 and 16.8% for wave III and V latencies, respectively, controlling for sex and HOME. PbB and gender effects on wave V are illustrated in Fig. 4. BAEPs recorded from three girls with varying PbB levels are shown in Fig. 5. The HOME score increased linearly with

TABLE 3
SLOW WAVE VOLTAGE DURING ACTIVE SENSORY CONDITIONING: SAMPLE MEANS AND EXPLORATORY ANALYSIS OF RECORDING SITE AND MEASUREMENT EPOCH

(a) Mean and standard error of slow wave voltage (μV)

	Epoch	
Site	500–1000	1000–15,000
Fz	−13.17, 1.18	−11.00, 1.12
Cz	−7.97, 0.91	−9.87, 0.97
Pz	1.67, 0.95	−1.81, 0.60

(b) Multivariate contrasts of dependent variables

Effect	F	P	df_N, df_D
Site × epoch	15.10	0.00001	2,44
Site	51.46	3×10^{-12}	2,44
Epoch	1.91	0.17	1,45

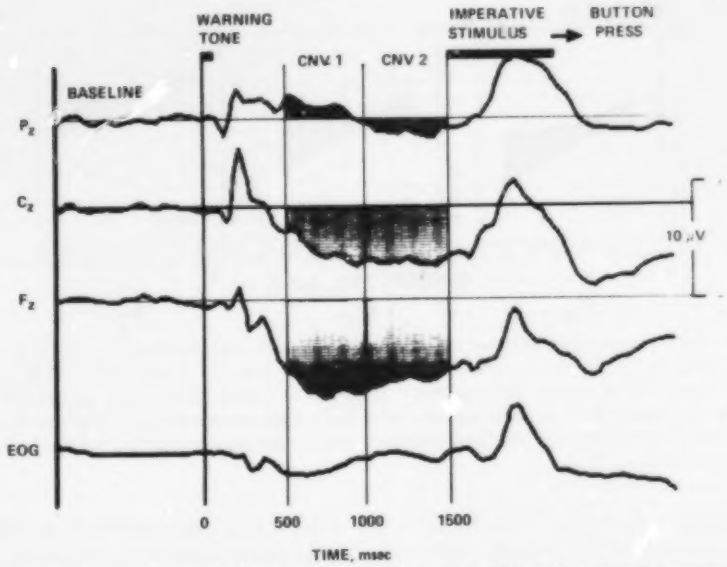

FIG. 2. Summary averages of slow potentials observed in children during active sensory conditioning. Horizontal bars above the averages depict the intervals during which warning and imperative (cartoon off) stimuli were presented. The cartoon was restored as soon as the subject pressed a button. Measurement intervals for slow potentials, designated as CNV1 and CNV2, are indicated by vertical lines.

wave V latency. No significant Pb effect on BAEP latency was observed when current PbB was used.

Pattern-reversal visual evoked potentials. Figure 6 illustrates PREP waveforms recorded from a typical subject. Table 5 shows the mean, standard error, and range of observed PREP measures. Exploratory multivariate and stepdown tests were done to evaluate the relationships of PREP measures, original PbB, and

TABLE 4

EXPLORATORY ANALYSES OF SLOW WAVE VOLTAGE AT DIFFERENT RECORDING SITES DURING ACTIVE CONDITIONING AND USING CURRENT PbB LEVELS

	Multivariate			Univariate *P* values					
Effect	*F*	*P*	df_N, df_D	Fz 500–1000 msec	Cz 500–1000 msec	Pz 500–1000 msec	Fz 1000–1500 msec	Cz 1000–1500 msec	Pz 1000–1500 msec
Int[a]	1.37	0.12	30,125.7	0.25	0.88	0.62	0.12	0.54	0.29
Main[b]	1.08	0.36	30,146.9	0.23	0.07	0.17	0.23	0.15	0.018
Keep									SES 0.0009 MIQ 0.005
PbB	2.85	0.02	6,39	0.15	0.37	0.71	0.025	0.046	0.002

[a] Int—Interaction terms—PbB5 × age, PbB5 × HOME, PbB5 × MIQ, PbB5 × sex, PbB5 × SES.
[b] Main—Main effects—age, HOME, MIQ, sex, SES.

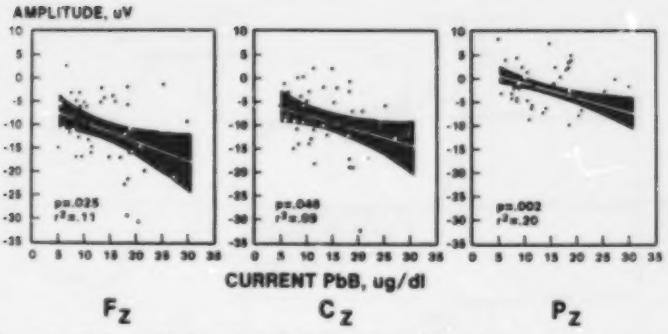

FIG. 3. Slow potential amplitude at frontal (Fz), central (Cz), and parietal (Pz) scalp locations recorded during active sensory conditioning and plotted as a function of blood lead (PbB) levels of children on the day of testing. Slow potential negativity increased linearly with current PbB at all recording sites. Mean slow potential voltage during the half-second preceding the imperative stimulus was measured. Scatter plots of data from individual subjects are shown with 95% confidence intervals for derived regression lines.

demographic variables. Results of these analyses are summarized in Table 7. Although none of the overall multivariate tests were significant, univariate tests indicated that N2 latency decreased and N1P1 amplitude increased linearly with original PbB levels. N1P1 amplitude also varied significantly with SES. Figure 7 illustrates the observed relationship of original PbB, N2 latency, and N1P1 amplitude. Similar results were obtained using current PbB values, except that N2 latency did not vary with PbB5.

DISCUSSION

Sensory conditioning. The linear relationship of PbB and SW voltage during passive sensory conditioning observed in the original evaluation (Otto *et al.*, 1981)

TABLE 5
SUMMARY OF BRAINSTEM AUDITORY AND PATTERN-REVERSAL VISUAL EVOKED POTENTIAL DATA IN 5-YEAR FOLLOW-UP STUDY

	N	Mean	SE	Min	Max
BAEP					
Wave I latency (msec)	45	1.77	0.025	1.49	2.33
Wave III latency	45	3.94	0.028	3.61	4.45
Wave V latency	45	5.72	0.036	5.30	6.33
Interpeak latency V-I	45	3.95	0.032	3.50	4.43
Interpeak latency V-III	45	1.78	0.022	1.45	2.17
Interpeak latency III-I	45	2.17	0.021	1.90	2.43
PREP					
N1 latency (msec)	43	69.7	0.60	62.5	79.5
P1 latency	43	101.7	0.94	92.0	118.5
N2 latency	43	149.5	3.68	104.5	198.5
N1P1 amplitude (μV)	43	24.3	1.20	9.75	46.6

TABLE 6
EXPLORATORY ANALYSIS OF BRAINSTEM AUDITORY EVOKED POTENTIAL LATENCIES: F, $P_{,df_N, df_D}$

	Multivariate		Wave I		Wave III		Wave V		IPL V–I		IPL V–III		IPL III–I	
Int[a]	0.85, 0.62	15,77.7	1.10, 0.38	5, 33	0.48, 0.79	5, 33	0.26, 0.93	5, 33	1.40, 0.25	5, 33	0.64, 0.67	5, 33	1.37, 0.26	5, 33
Main[b]	1.75, 0.055	15,90.2	.55, .74	5, 38	3.13, 0.018	5, 38	4.77, 0.002	5, 38	3.16, 0.018	5, 38	1.69, 0.16	5, 38	2.35, 0.06	5, 38
Drop	All		All		SES 0.00, 0.97	1, 38	SES 0.23, 0.64	1, 38	Age 0.55, 0.46	1, 38	All		All	
					HOME 0.39, 0.54	1, 39	MIQ 0.49, 0.49	1, 39	MIQ 0.47, 0.49	1, 39				
					MIQ 4.04, 0.051	1, 40	Age 2.89, 0.10	1, 40	SES 0.72, 0.40	1, 40				
					Age 3.44, 0.07	1, 41			HOME 2.33, 0.13	1, 41				
Keep					Sex 7.19, 0.01	1, 42	Sex 16.90, 0.0002	1, 41	Sex 11.81, 0.001	1, 42				
							HOME 5.21, 0.03	1, 41						
PbB1	2.32, 0.09	3,4?	2.15, 0.15	3, 51	9.06, 0.004	1, 41	8.67, 0.005	1, 41	1.29, 0.26	1, 42	0.14, 0.71	1, 43	2.16, 0.15	1, 44

[a] Int—Interactions of PbB1 with age, SES, MIQ, sex, and HOME.
[b] Main—Main effects of age, SES, MIQ, sex, and HOME.

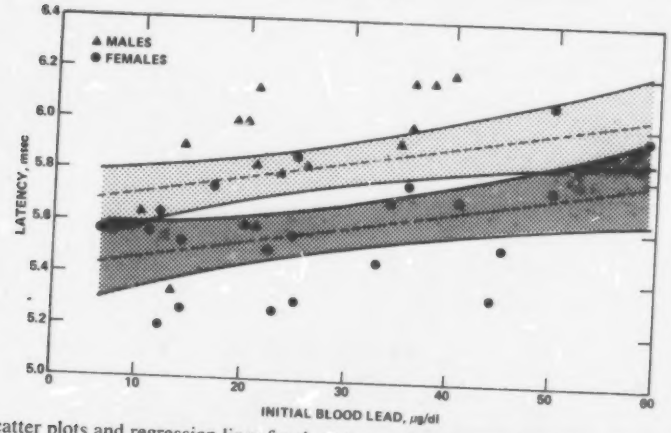

FIG. 4. Scatter plots and regression lines for the latency of component V of the auditory brainstem evoked potential plotted as a function of initial blood lead levels obtained 5 years earlier. Wave V latencies of males (upper regression line) were significantly longer than females (lower line). Wave V latencies increased linearly with initial blood lead levels. For each regression line, 95% confidence bands are also plotted.

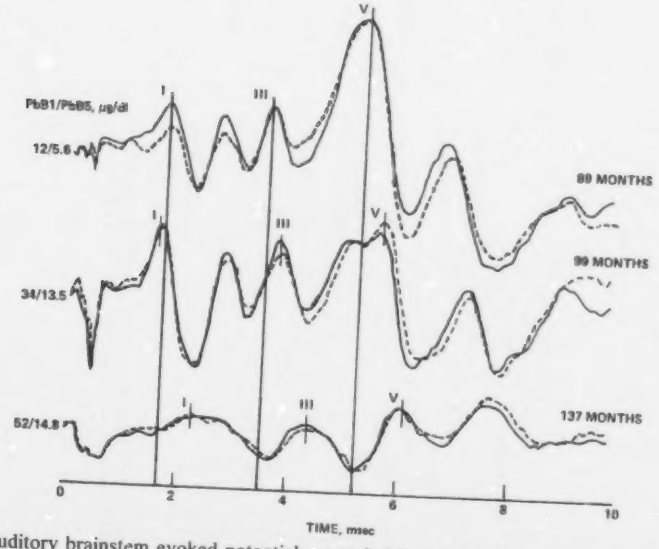

FIG. 5. Auditory brainstem evoked potentials recorded from three girls with varying initial blood lead (PbB1) levels. Replicate averages of 2000 trials recorded binaurally using 60 dBSL clicks are shown for each child. Latencies of waves III and V increased linearly with PbB1. Note that blood lead levels (PbB5) of all girls were below 15 µg/dl at the time of BAEP recording.

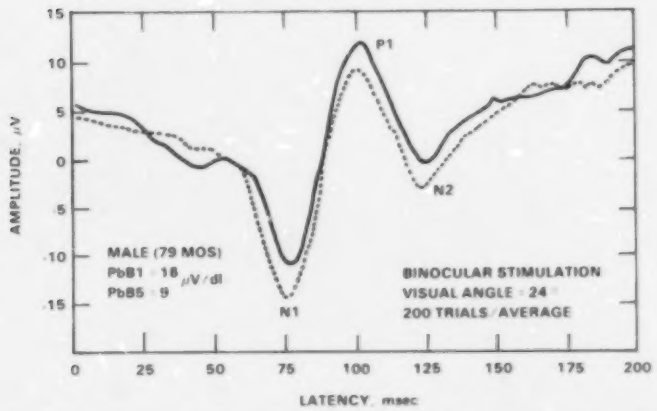

FIG. 6. Pattern-reversal visual evoked potentials recorded from a typical subject. Replicate waveforms were obtained from each child using binocular stimulation from black and white squares subtending 24° visual angle, 90% contrast, and reversing twice per second. Latencies of N1, P1, and N2 components and N1P1 amplitude were measured.

and the 2-year follow-up (Otto *et al.*, 1982) was not evident in the 5-year follow-up confirmatory test. Exploratory analyses indicated complex relationships of lead, gender, socioeconomic status, maternal IQ, HOME scores, and SW voltage that were not found in previous studies. SW voltage does not appear to be a culture-free measure in children, particularly at the postcentral recording site. Further study is necessary to clarify the relationship of SW voltage, conditioning, and sociodemographic covariates which may influence the effects of Pb exposure on CNS function in children (cf.Schroeder *et al.*, 1985; EPA, 1985).

Negative results of the confirmatory SW analysis suggest two possibilities. First, abatement of Pb contamination in the environment of these children (Milar and Mushak, 1982) and concomitant reduction in body Pb burden may have reversed or ameliorated CNS effects previously observed. This interpretation is consistent with IQ data from these children—i.e., a Pb-related IQ deficit was observed during the initial evaluation, but no significant Pb effect was found 5 years later (Schroeder *et al.*, 1985). Significant Pb-related effects observed in exploratory analyses of BAEP latencies, PREP measures, and SW voltage during active conditioning, however, are not compatible with this interpretation.

Alternatively, the passive conditioning test may not be sensitive to toxicant insult in older children. We have previously found (Otto *et al.*, 1981) that slow potential changes are not elicited in adults by the passive conditioning paradigm. In the present study, SW amplitude was considerably greater in the active than passive conditioning tests, consistent with an early report of slow negative potentials in humans during sensorimotor conditioning (Walter *et al.*, 1964). However, slow wave negativity during active conditioning increased directly with current PbB levels at all three scalp recording sites. It should be noted, furthermore, that the direction of this effect is consistent with the predicted regression function

TABLE 7

EXPLORATORY ANALYSES OF PATTERN-REVERSAL VISUAL EVOKED POTENTIAL LATENCIES AND AMPLITUDE: F, P, df_N, df_D

	Multivariate latency		N1 latency		P1 latency		N2 latency		N1P1 amplitude	
Int[a]	1.03, 0.43	15, 72.7	1.20, 0.33	5, 31	0.44, 0.82	5, 31	1.34, 0.28	5, 31	0.62, 0.68	5, 31
Main[b]	0.95, 0.51	15, 85.2	1.12, 0.37	5, 36	0.64, 0.67	5, 36	0.50, 0.77	5, 36	3.03, 0.022	5, 36
Drop	All		All		All		All		Sex 0.00, 0.95	1, 36
									HOME 0.01, 0.93	1, 37
									MIQ 0.04, 0.84	1, 38
Keep									Age 2.87, 0 10	1, 39
PbB1	1.87, 0.15	3,39	.09, 0.77	1, 41	1.03, 0.32	1, 41	5.65, 0.022	1, 41	SES 12.86, 0.0009	1, 40
									7.22, 0.01	1, 40

[a] Int—Interactions of PbB1 with age, SES, MIQ, sex, and HOME.
[b] Main—Main effects of age, SES, MIQ, sex, and HOME.

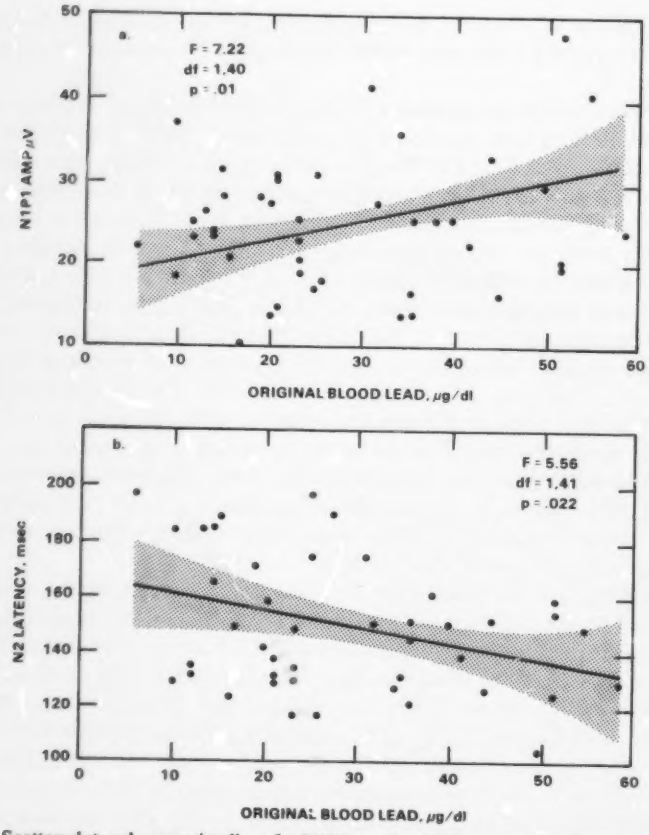

FIG. 7. (a) Scatter plot and regression lines for N1P1 amplitude of the pattern-reversal visual evoked potential as a function of original PbB level. N1P1 amplitude increased linearly with PbB. (b) Scatter plot and regression line for N2 latency as a function of original PbB level. N2 latency decreased inversely with PbB. For both regression lines, 95% confidence bands are plotted.

for 95-month-old children obtained in the 2-year follow-up study (Otto *et al.*, 1982, Fig. 2). Thus the passive conditioning test appears to be an ineffective method for toxicity testing in older children as well as adults.

Visual evoked potentials. Results of the exploratory analysis of pattern-reversal visual evoked potentials were contrary to predictions. Although significant effects of original PbB on N1P1 amplitude and N2 latency were found, the overall multivariate test was not significant. Interpretation of univariate stepdown tests is thus problematic. The wide variability of N2 latency measures also clouds the data. Moreover, the parameter expected to vary with Pb exposure—P1 latency—failed to show any significant Pb effect. Although the components differ, the direction of effect in our findings is consistent with Ewert *et al.* (in press), who reported decreased P1 latency with increasing PbB in Nordenham children. Our

results and those of Ewert *et al.* are contrary to the findings of Sborgia *et al.* (1983), who reported increased PREP latencies in Pb-exposed workers relative to controls.

An important factor to consider is that the PREP in humans reflects primarily photopic rather than scotopic visual function (Sokol, 1976). The studies of Bushnell *et al.* (1977) and Fox and Wright (1982) suggest that scotopic vision is selectively affected by Pb. Thus, the PREP under light-adapted conditions may not be a particularly sensitive index of Pb effects on visual function in humans.

Brainstem auditory evoked potentials. Results of auditory brainstem testing were more consistent with predictions—i.e., increases in wave III and V latencies were associated with increases in original PbB levels. Failure to find any Pb effect on wave I latency suggests that the effect in the auditory pathway is rostral to the cochlear nucleus, although one would expect to see a Pb effect on interpeak latencies (V-I, V-III, or III-I) if this were the case. The procedure used to set click intensity may account for this discrepancy. Adjusting click intensity so that all subjects perceived stimuli at the same sensation level should have compensated for any end-organ deficit and thus may have obscured a possible Pb effect on wave I. The PbB-related increase in latencies of BAEP waves III and IV, therefore, could be either central or peripheral in origin. Further study is necessary to clarify this paradoxical finding.

Hearing deficits have been reported in several studies of workers occupationally exposed to lead, particularly at blood Pb levels above 70 μg/dl (cf. Repko and Corum, 1979). Elevated hearing thresholds have usually been observed at high frequencies between 4000 and 8000 Hz, although Repko *et al.* (1975, 1978) have found hearing deficits across a broader range of frequencies (500 to 8000 Hz). Repko and Corum (1979) have criticized previous studies for small size, limited control of age effects, and limited information concerning the noise exposure of workers. Hearing deficits were associated in some cases with frank symptoms of lead poisoning and in most cases with PbB levels considerably higher than those observed in the present study of children.

The effect of lead on auditory function in children has not been systematically studied. Auditory processing deficits have been reported in cases of acute lead poisoning (Jenkin and Mellins, 1954) as well as asymptomatic exposure (Perino and Ernhart, 1974; Needleman *et al.*, 1979). The latter studies examined complex aspects of expressive and receptive speech perception, however, rather than simple hearing thresholds. Needleman *et al.* (1979), for instance, compared the performance of children with high and low dentine Pb levels on the Seashore rhythm test, token test, sentence repetition test, and verbal subtests of the WISC-R. These tests are designed to assess language comprehension and memory.

The linear relationship of BAEP latency and PbB levels observed in the present study is the first direct evidence of auditory effect in children with asymptomatic Pb exposure. Laughlin *et al.* (1983) reported reduced amplitude of auditory evoked potentials in young monkeys with PbB levels of 35 to 45 μg/dl, comparable to exposure levels of children in the present study. Complex vowel–consonant phonemes derived from human speech were used in the monkey study, however, precluding any meaningful comparison of data.

Results of the present study do not indicate that hearing thresholds of children were altered by lead exposure. Hearing thresholds derived from 2-kHz pure tone screening did not vary significantly with original Pb levels, although a systematic audiometric evaluation across a wide range of frequencies was not made. The BAEP is most sensitive to hearing loss in a fairly restricted range (2 to 4 kHz). It should be noted that abnormal BAEP latencies in multiple sclerosis patients are frequently observed in the presence of normal audiometric findings (cf. Stockard *et al.*, 1980). Although the Pb-related increases in BAEP latency observed in the present study do not appear to be associated with simple hearing loss, further study is needed to determine whether lead exposure alters hearing thresholds in children.

Finally, the linear relationship of PbB and BAEP latency should be emphasized. The apparent shift in BAEP latencies associated with Pb exposure was relatively small—about 0.3 msec between 10 and 60 μg/dl—and was within clinically normal limits for most children in the sample. The important point is that a progressive increase in BAEP latency occurred with increasing Pb exposure history. Examination of residuals from the linear analysis did not indicate the presence of any higher order effects. A continuous effect was thus apparent across the entire range of PbB levels consistent with previous SW voltage (Otto *et al.*, 1981, 1982) and nerve conduction velocity (Landrigan *et al.*, 1976) findings in children.

CONCLUSIONS

1. Slow wave voltage during *passive* conditioning did not vary as a function of blood lead history or age in children 5 years after original testing. Preliminary evidence suggests, however, that SW negativity during *active* conditioning increases with current PbB level. Active conditioning thus appears to be more sensitive than passive conditioning [illegible] neurotoxicity testing. In view of these findings, we recommend that the passive conditioning test be used only in subjects who are very young or physically unable to make reliable behavioral responses.

2. Results of visual evoked potential testing were contrary to prediction. Results of other VEP studies in humans and animals exposed to Pb have also been contradictory. Further studies of VEPs in humans and animals under scotopic and photopic conditions are needed to clarify the relationship of lead exposure and visual function.

3. While the functional significance of slow wave changes associated with Pb exposure in this and previous studies (Otto *et al.*, 1981, 1982) is uncertain, the interpretation of BAEP results is straightforward. The slowing of nerve conduction in the auditory pathway (as indexed by BAEP latencies) has been unambiguously related to pathological lesions (Starr, 1977; Starr *et al.*, 1978) and nonspecific demyelinating diseases such as multiple sclerosis (Stockard *et al.*, 1980). The observed Pb-related increases in BAEP latencies are thus suggestive of subclinical pathology of the auditory pathway rostral to the cochlear nucleus, although peripheral impairment cannot be ruled out. A comprehensive behavioral and electrophysiological evaluation of auditory function in lead-exposed humans

or animal models is needed to clarify the origin of this effect. On the other hand, the preliminary nature of the present BAEP findings must also be emphasized. Further studies have been undertaken to clarify these findings in an independent sample of children at risk for lead poisoning.

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